
Disruption of mesoderm formation during cardiac differentiation due to developmental exposure to 13-cis-retinoic acid.

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Public Summary:

Scientific Abstract:

13-cis-retinoic acid (isotretinoin, INN) is an oral pharmaceutical drug used for the treatment of skin acne, and is also a known teratogen. In this study, the molecular mechanisms underlying INN-induced developmental toxicity during early cardiac differentiation were investigated using both human induced pluripotent stem cells (hiPSCs) and human embryonic stem cells (hESCs). Pre-exposure of hiPSCs and hESCs to a sublethal concentration of INN did not influence cell proliferation and pluripotency. However, mesodermal differentiation was disrupted when INN was included in the medium during differentiation. Transcriptomic profiling by RNA-seq revealed that INN exposure leads to aberrant expression of genes involved in several signaling pathways that control early mesoderm differentiation, such as TGF-beta signaling. In addition, genome-wide chromatin accessibility profiling by ATAC-seq suggested that INN-exposure leads to enhanced DNA-binding of specific transcription factors (TFs), including HNF1B, SOX10 and NFIC, often in close spatial proximity to genes that are dysregulated in response to INN treatment. Altogether, these results identify potential molecular mechanisms underlying INN-induced perturbation during mesodermal differentiation in the context of cardiac development. This study further highlights the utility of human stem cells as an alternative system for investigating congenital diseases of newborns that arise as a result of maternal drug exposure during pregnancy.

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